

Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-9, 11, 13-16, 20-34, 36, 38-41, 45-50, and 73-84 are pending, with claims 1, 26, and 73 being the independent claims. Claims 10, 12, 17-19, 35, 37, 42-44, and 51-72 are canceled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue the canceled subject matter in related cases. Claims 7, 8, 15, 16, 23, 24, 32, 33, 40, 41, 48, 49, and 78 are withdrawn. Claims 1, 2, 4-5, 13, 15, 20, 26, 27, 29, 30, 33, 38, 49, and 73-78 are amended. Claims 79-84 are newly submitted. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Support for Amendments

Support for the amendments to the claims can be found throughout the original claims and the specification. In particular, support for the amendments in claims 1, 26, 73, and 79-84 can be found at paragraphs [00026], [00040]-[00043], [00046]-00050], and [00075]. Support for the amendments in claims 2 and 27 can be found at Table 6.

III. *Premature Final Rejection*

The Examiner has allegedly made the Office Action final in accordance with M.P.E.P. § 706.07(a). Applicants submit that the finality of the instant Office Action is premature for at least the following reasons, and respectfully request that the finality be withdrawn.

According to M.P.E.P. § 706.07(a):

A second or any subsequence action on the merits in any application or patent undergoing reexamination proceedings will not be made final if it includes a rejection, on newly cited art, other than information submitted in an information disclosure statement filed under 37 C.F.R. 1.97(c) with the fee set forth in 37 C.F.R. 1.17(p), of any claim not amended by applicant or patent owner in spite of the fact that other claims may have been amended to require newly cited art.

Applicants submit that the Examiner newly cited three references in this Office Action that were not submitted in the information disclosure statements by Applicants. The newly cited references are U.S. Publication No. US 2003/0191286 A1, filed January 2, 2003 and published October 9, 2003 ("Hildebrand"), U.S. Publication No. US 2004/0253632 A1, filed May 16, 2001 and published December 16, 2004 ("Rhode"), and U.S. Publication No. 2004/0072262 A1, filed October 11, 2002 and published April 15, 2004 ("Montero-Julian"). Applicants respectfully point out that rejected claims 3, 6, 9, 11, 14, 21, 22, 25, 28, 31, 34, 36, 39, 46, 47, and 50 are original claims and thus have never been amended. Accordingly, the instant Final Office Action has not allowed a "clear issue between the Applicant[s] and the Examiner" to develop as well as an opportunity for the Applicants to amend the claims in view of the cited references in accordance with M.P.E.P. § 706.07.

Applicants submit that for the aforementioned reasons, Applicants have not received a "full and fair hearing," and respectfully request that the Examiner consider each of the aforementioned arguments and withdraw the finality of all outstanding rejections.

IV. Rejection Under 35 U.S.C. §112, Second Paragraph.

The Examiner has rejected claims 13, 14, 38, and 73-77 for allegedly being indefinite. The Examiner rejected claims 13, 14, and 38 for depending directly or indirectly from a canceled claim. Applicants thank the Examiner for bringing this issue to our attention. The claims 13 and 14 are amended to depend from claim 1, rendering the rejection moot.

The Examiner also rejected claims 73-77 for allegedly being indefinite "because it is not clear what it meant." Office Action at page 3. The Examiner further stated that:

It is clear from the instant disclosure that a 'system' is not equivalent to a 'kit,' such kit may also comprise the same elements as the system, including instructions. The specification does not provide disclosure of what elements comprise a 'system' besides the ingredients common to both a system and a kit.

Office Action at Page 3. Applicants respectfully traverse the rejection.

According to M.P.E.P., "[i]n reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent." M.P.E.P. §2173.05(a)

Contrary to the Examiner's assertion, Applicants respectfully note that it is clear from the specification that the term "system" is interchangeable with the term "kit." Paragraph

[00057] of the specification as originally filed shows that "the invention provides *systems*, *kits*, and *assays* for evaluating putative MHC-binding peptides to determine whether such fragments can be incorporated into a ternary complex with an MHC monomer or modified MHC monomer." Throughout the specification, Applicants then used the term "system" interchangeably with "kit." For example, dependent claim 74 further includes "instructions" with the claimed system. Therefore, the words "system for identifying an MHC-binding peptide for an MHC monomer, or modified MHC monomer" is definite and precise as the specification clearly defines its scope and a person of ordinary skill in the art would easily understand boundary of the claim. Applicants nonetheless have amended those claims to recite "kit" simply in an effort to expedite prosecution. Accordingly, Applicants respectfully request that the rejection be withdrawn.

V. The Currently Pending Claims are Non-Obvious

The Examiner rejected claims 1-6, 9, 11, 13, 17, 20-22, 25-31, 34, 36, 38, 42, 45-47, and 50 under 35 U.S.C. § 103(a) over International Publication No. WO 92/07952 A1, filed October 30, 1991 ("Rothbard") in view of Hildebrand, Rhode, and Montero-Julian.

Applicants respectfully disagree and traverse the rejection.

Solely to facilitate prosecution of this application and not in acquiescence of the Examiner's rejection, Applicants amended claims 1, 2, 4, 5, 20, 26, 27, 29, and 30 and canceled claims 17 and 42. Insofar as the rejection applies to the amended claims, however, Applicants assert that the pending claims are not rendered obvious over the cited references.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re*

Piasecki, 745 F.2d 1468, 1471-73 (Fed. Cir. 1984). As set forth in *Graham v. John Deere Co. of Kansas City*, "[u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." 383 U.S. 1, 17 (1966).

In addition, the Examiner must show reasons, explicit or otherwise, that would compel one of ordinary skill in the art to combine the references in order to make and use the claimed invention. To determine whether there is "an apparent reason to combine" the known elements in the way an application claims,

it will be necessary. . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art. . . . To facilitate review, this analysis should be made explicit.

Id. at 14; *see also* Memorandum from the United States Patent and Trademark Office, "Supreme Court decision on *KSR Int'l. Co. v. Teleflex, Inc.*," (May 3, 2007) ("The Court did not totally reject the use of 'teaching, suggestion, motivation' as a factor in the obviousness analysis. . . . [I]n formulating a rejection. . . based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

"There is no suggestion to combine . . . if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999); *see also KSR*, U.S. LEXIS 4745 at *34 (reaffirming "the corollary principle that when the prior art teaches away from combining certain known

elements, discovery of a successful means of combining them is more likely to be nonobvious") (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, *or would be led in a direction divergent from the path that was taken by the applicant . . .*" *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (*emphasis added*).

In view of the current state of the law, Applicants assert that the cited references fail to teach or suggest the claimed methods and provide no apparent reason to combine the references cited by the Examiner to arrive at the claimed invention. Applicants further assert that a person of ordinary skill in the art would have no reasonable expectation of success in making the claimed invention.

The currently pending claims are directed to a method for identifying an MHC-binding peptide or measuring relative affinity for an MHC binding peptide. The method comprises incubating under a liquid phase condition a ternary complex comprising at least one HLA-A2 monomer having bound thereto a template MHC-binding peptide and beta-2 microglobulin, and wherein said monomer is produced in an expression system selected from the group consisting of a prokaryotic system, a yeast system, a plant system, and an insect system; an excess amount of a first competitor peptide, and a tracer MHC-binding peptide tagged with a detectable label, wherein the template peptide has a lower affinity than the tracer peptide for the monomer. Especially, the amended claims now require that the HLA-A2 monomer is recombinantly produced in an expression system selected from the group consisting of a prokaryotic, yeast, plant, and insect expression system.

Rothbard discloses an assay “for measuring affinity of small molecular weight organic molecules and peptides to an MHC glycoprotein.” Rothbard at Abstract.

Specifically, Rothbard discloses various assays utilizing the MHC class II glycoproteins. In addition, Rothbard notes that the MHC glycoprotein can form an empty pocket without any bound peptide, which is a feature limited to an MHC class II glycoprotein. *See id* at page 4.

As acknowledged by the Examiner in the Office Action, therefore, Rothbard fails to teach the HLA-A2 monomer. *See* Office Action at page 4.

Hildebrand discloses production of a recombinant MHC class I molecule, such as HLA-A2 monomer. However, Hildebrand discloses a recombinant MHC class I glycoprotein produced only in mammalian cell lines, but not in prokaryotic, yeast, plant, or insect expression systems. Therefore, Hildebrand provides no disclosure of the specific HLA-A2 monomer used in Applicants' claimed method.

Applicants respectfully note that rejections of claims 17 and 42 over Rothbard in view of Hildebrand and Rhode have been rendered moot because all rejected claims have been canceled.

Applicants also respectfully note that Montero-Julian is not applicable art. As the Examiner properly acknowledged in the Office Action, Montero-Julian constitutes art only under 35 U.S.C. § 102(e). Office Action at page 6. Applicants submit that Montero-Julian is not an applicable reference under 35 U.S.C. §103(c). 35 U.S.C. §103(c) provides:

(1) Subject matter developed by another person, which qualifies as prior art only under one or more of **subsections (e), (f), and (g) of section 102 of this title**, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was

made, owned by the same person or subject to an obligation of assignment to the same person.

(2) For purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person if -

(A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made;

(B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

(3) For purposes of paragraph (2), the term "joint research agreement" means a written contract, grant, or cooperative agreement entered into by two or more persons or entities for the performance of experimental, developmental, or research work in the field of the claimed invention.

(See 35 U.S.C. §103(c), emphasis added.)

In order to show that the present application and Montero-Julian are owned by the same party or subject to obligation to assignment to the same party at the time the claimed invention was made, Applicants hereby submit the assignment of the present application (Exhibit A) and the assignment of Montero-Julian (Exhibit B). The assignment of Montero-Julian was executed from inventors to Beckman Coulter Inc. on November 5, 2002, then was recorded on the United States Patent and Trademark Office ("USPTO") on February 10, 2003 by wheel/frame number 013742/0414. The assignment of the present invention was executed on May 7 or 11, 2004 from inventors to Beckman Coulter, Inc. and recorded on July 29, 2004 at the USPTO under wheel/frame number 015616/0021. Because the reference was owned at the time of the invention of the present application by Beckman Coulter, Inc. or subject to the

assignment to Beckman Coulter, Inc., 35 U.S.C. §103(c) provides that the reference may not be applied against the present application. Accordingly, Applicants respectfully note that only Rothbard and Hildebrand are considered in this Reply.

With respect to Rothbard and Hildebrand, the Examiner has alleged the following:

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the soluble HLA-A2 monomers disclosed by [Hildebrand] as the MHC molecule in the method taught by [Rothbard].

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because [Rothbard] teaches a method of determining binding affinity of a candidate peptide for a specific MHC molecule, and [Hildebrand] discloses that HLA-A2 is a specific MHC molecule and further discloses methods to make soluble MHC molecule.

Office Action at page 4.

In view of the claim amendments, Applicants assert that all the claimed elements are not taught or suggested in the references. Both Rothbard and Hildebrand fail to teach the HLA-A2 monomer recombinantly produced in a prokaryotic, plant, yeast, or insect expression system.

Even assuming, *arguendo*, the references taught each and every element of the claim, there would have been no apparent reason for one of ordinary skill in the art to combine Rothbard with Hildebrand. As noted above, Rothbard disclosed MHC class II glycoprotein, which has a structure of "noncovalent dimers of α and β chains." *See* Nepom *et al.*, *Arthritis & Rheumatism*. 46(1), 5-12, 6 (2002) ("Exhibit C" hereinafter). However, Hildebrand disclosed an MHC class I molecule, which is comprised of $\alpha 1$, $\alpha 2$, $\alpha 3$ domains and beta-2 microglobulin. *See* paragraph [0024]. Therefore, these MHC class I and MHC class II

molecules are structurally as well as functionally different. Indeed, it was well known in the art that different approaches are necessary for MHC class I and class II molecules. *See* Exhibit C at page 6. In particular, Exhibit C notes that "[s]tructural differences between class I and class II molecules necessitate different approaches to tetramer design and use." *Id.* For example, it was known that an MHC class II molecule cannot be renatured to form a ternary structure while MHC class I molecule can be efficiently renatured in the presence of antigenic peptides to yield a ternary complex. *Id.* Therefore, a person of ordinary skill in the art would not have thought that the MHC class I molecule in Hildebrand can replace the MHC class II molecule used in Rothbard's assay using the MHC class II molecule.

Furthermore, there is no reasonable expectation of success in combining the references of Rothbard and Hildebrand. It was well known in the art that, as shown in Exhibit C, MHC class I molecule cannot simply replace MHC class II molecule due to its structural differences. Furthermore, the MHC class I glycoprotein produced in mammalian cells similar to Hildebrand cannot be used in a sensitive assay system such as Rothbard to detect binding of and measure an affinity of an MHC binding peptide. Indeed, Hildebrand notes an example of such problems that:

One of ordinary skill in the art would note the importance, given the present invention, that cells expressing endogenous class I MHC molecules may spontaneously release MHC into solution upon natural cell death. In cases where this small amount of spontaneously released MHC is a concern, the transfected class I MHC molecule can be "tagged" such that it can be specifically purified away from spontaneously released endogenous class I molecules in cells that express class I molecules.

Paragraph [0084].

Unlike Hildebrand, the prokaryotic cells transformed with a vector encoding an HLA-A2 monomer may not express any endogenous MHC glycoprotein because the prokaryotic cells lack endogenous genes encoding the MHC molecules. This property effectively eliminates cumbersome steps of removing the endogenously expressed MHC glycoprotein from the recombinantly produced MHC monomer. In view of the problems readily apprehended from the cited references, a person of ordinary skill in the art would not have any reasonable expectation of success in making or using the claimed invention.

Applicants also assert that the Examiner used hindsight in combining the references of the instant rejection. It is not permissible to pick and choose among isolated disclosure in the references to deprecate the claimed invention. As discussed above there is not motivation to combine the references and there is no reasonable expectation of success when combining the references. Thus, it appears that hindsight reconstruction was used in formulating the instant rejection.

For the reasons set out above, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Reconsideration and withdrawal of this rejection is requested.

Conclusion

All of the stated grounds of objection and rejections have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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